Phase I Bladder Cancer Gene Therapy

Technical Abstract

Bladder cancer is a desirable target for gene therapy because of the ease of accessibility via cystoscopy, direct visualization of tumor, and sampling with biopsy and urine cytology. Standard therapy for superficial disease results in 30% of patients not responding to therapy, and the long-term risk of developing invasive and potentially metastatic disease is 30%-50%. Muscle-invasive cancer can be controlled by radical cystectomy, only if the tumor is completely excised, and contemporary series indicate 5-year survival rates of 50%-60%. These data provide a strong rationale for novel treatments that may lead to incremental gains in efficacy.

Baylor College of Medicine has established an extensive program of gene therapy for solid tumors and hematologic malignancies. There is extensive institutional experience with "suicide gene therapy" with adenoviral-mediated Herpes Simplex Virus-thymidine kinase (HSV-*tk*) plus the pro-drug, ganciclovir (GCV) or acyclovir, in patients with prostate and ovarian cancer, retinoblastoma, brain tumors and metastatic colon cancer. In the first 18 patients treated, only one experienced significant grade 3 or grade 4 toxicity with reversible thrombocytopenia and hepatotoxicity. Over 110 patients have been treated in prostate cancer trials with observation of an antitumor effect mediated by necrosis, apoptosis and an immune response with documented decreases in PSA.

Our preclinical *in vitro* and *in vivo* studies with Ad/HSV-tk in bladder cancer document efficient delivery of the transgene with direct injection, clear evidence of efficacy and a survival benefit and safety in the animal model. The purpose of this study is to conduct a Phase I clinical trial to extend our preclinical studies involving *in situ* suicide gene therapy for bladder cancer. The primary outcome measure is one of safety, as this particular vector and strategy has not been applied yet in the setting of bladder cancer. Eligible patients will have either failed conventional intravesical therapy for superficial disease or require radical cystectomy for refractory superficial or invasive cancer. We will inject Ad/HSV-*tk* virus into the index bladder tumor under direct vision via cystoscopy and follow this with 14 days of intravenous ganciclovir. We will observe carefully for any toxic side effects. Two weeks after completing GCV, patients will undergo transurethral resection or radical cystectomy and we will determine the effect of the gene therapy on the tumor and the local and systemic immune response. Patients will be followed lifelong for evidence of recurrence of their cancer.

In the long run, pro-drug suicide gene therapy can be used as cytoreductive primary therapy or as neoadjuvant therapy prior to transurethral resection or radical cystectomy in order to optimize control of local regional primary tumors. In addition, there is a rationale of combination therapy that may improve the therapeutic window and safety of current approaches combining extensive transurethral resection, chemotherapy and radiotherapy. *In situ* suicide gene therapy may also be utilized to induce local and systemic immunity - the so-called distant bystander effect.